

# Efficacy and safety of aceclofenac in osteoarthritis: A meta-analysis of randomized controlled trials

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## Abstract

**Objective:** To analyze the effects on pain, function, and safety of aceclofenac compared with other nonsteroidal anti-inflammatory drugs (NSAIDs) or pain relief medications in patients with osteoarthritis.

**Material and Methods:** Two investigators independently searched the database. We included randomized controlled trials evaluating efficacy and/or safety of aceclofenac compared with control interventions (NSAIDs or acetaminophen) in patients with osteoarthritis. We did not include placebo, opioid analgesics, NSAID combinations, and topical analgesics for the control groups. We summarized the efficacy data as standardized mean differences (SMD) with 95% confidence intervals (CI) and safety outcomes as risk ratios (RR) with 95% CI using the inverse variance random effect model. We assessed the heterogeneity by the  $I^2$  test. We used the GRADE approach to evaluate the quality of the evidence for all outcome parameters.

**Results:** We included 9 trials (8 double blind and 1 single blind) that evaluated pain (7 trials), function (8 trials) and safety (7 trials). We observed no significant difference in pain reduction between aceclofenac and control interventions [SMD:  $-0.30$  ( $-0.62, 0.01$ );  $I^2=88\%$ ; GRADE evidence- low]. Aceclofenac was more beneficial than control interventions in improving physical function [SMD:  $-0.27$  ( $-0.50, -0.03$ );  $I^2=88\%$ ; GRADE evidence- low]. We observed less gastrointestinal adverse events for aceclofenac than in control interventions [RR 0.69 (95% CI: 0.57, 0.83);  $I^2=12\%$ ; GRADE evidence- moderate]. We observed no difference in overall adverse events occurrence and dropout rate between aceclofenac and control interventions.

**Conclusion:** We observed that aceclofenac was beneficial over control analgesics for function improvement and to minimize gastrointestinal adverse events. Our findings could be biased due to the heterogeneity of the sample, the fact that the trials were small and methodological issues.

**Keywords:** Osteoarthritis, aceclofenac, pain, function, safety, meta-analysis

## Introduction

Osteoarthritis is one of the most common, chronic and progressive musculoskeletal disorders. It usually occurs after the ages of 50 (1-3). Prevalence of osteoarthritis increases with age and it affects 60% of men and 70% of women after the age of 65 (4). It particularly affects the knee and hip joints in elderly people (1). Primary symptoms are joint pain, stiffness, limited movement, and impaired quality of life. Progression of disease can lead to joint failure with pain and disability (1). Osteoarthritis is a degenerative joint disease that mainly involves the cartilage and many surrounding tissues. Osteoarthritis causes damage and loss of articular cartilage within the synovial joints, increases the thickness of the subchondral plate, and leads to remodeling of the subarticular bone, osteophyte formation, ligamentous laxity, weakening of periarticular muscles, synovial inflammation and cyst formation in the subchondral bone (1, 5). Synovial tissue cells and subchondral osteoblasts produce cytokines. IL-1 beta and the tumor necrosis factor (TNF)-alpha are key cytokines in the catabolic process of cartilage degradation (5, 6). Inflammatory cytokines provide essential biochemical signals that stimulate chondrocytes to release cartilage-degrading enzymes (2).

Current medical management of osteoarthritis includes pharmacological and non-pharmacological therapies. Nonsteroidal anti-inflammatory drugs (NSAIDs) and various analgesics are the cornerstone of osteoarthritis management. Most clinical guidelines recommend NSAIDs as a first-line treatment of mild to moderate pain in osteoarthritis (7). However, NSAIDs do not alter the natural course of the disease (2), as they only provide effective relief from symptoms such as pain and inflammation. Also, their chronic use is associated with upper gastrointestinal damage including mucosal erosion, ulcer, perforation, and hemorrhage (8-11).

Nonsteroidal anti-inflammatory drugs, including nonselective, preferential, and selective COX-2 inhibitors, are used for the treatment of osteoarthritis. One systematic review found diclofenac to be comparable to other NSAIDs in osteoarthritis. However, authors did not pool the data for meta-analysis and did not



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assess the heterogeneity (12). Da costa et al. (13), based on a recent network meta-analysis of placebo-controlled trials, suggested that diclofenac (150 mg/day) is the most effective NSAID improving both pain and function. On the other hand, van Walsem et al. (14), in a network meta-analysis observed that diclofenac (150 mg/day) is likely to be more effective in alleviating pain than celecoxib (200 mg/day), naproxen (1000 mg/day), or ibuprofen (2400 mg/day), and similar to etoricoxib (60 mg/day) (14). However, it was comparable to all other NSAIDs for improving physical function.

Though selective COX-2 inhibitors are more gastroprotective, they produce adverse cardiovascular outcomes (8, 9, 11, 15). Recent studies also raised concerns for cardiovascular safety of traditional NSAIDs (14, 16, 17). Cardiovascular risks of diclofenac and ibuprofen are comparable to those of coxibs (16, 17). Based on literature review, Ong et al. suggested the following order of NSAIDs selection: acetaminophen, ibuprofen, naproxen, and a combination of traditional NSAIDs with an opioid or acetaminophen. They suggested COX-2 inhibitors as an alternative to naproxen in patients with no cardiovascular risk factors. They recommended the use of lower-risk traditional NSAIDs as a first-line treatment, and more toxic NSAIDs in case of a poor response to the lower-risk treatment (18).

Aceclofenac, a phenylacetic acid derivative, is a preferential COX-2 inhibitor and an analogue of diclofenac. It has additional properties to inhibit the synthesis of inflammatory cytokines such as interleukin-1, TNF, and Prostaglandin E2 (19, 20). It provides symptomatic relief in a variety of painful conditions such as dental extraction, episiotomy, rheumatoid arthritis (RA), osteoarthritis, and ankylosing spondylitis (21, 22). It is an effective, well-tolerated, and well-accepted therapy for both acute and chronic inflammatory and degenerative diseases (23). Aceclofenac is one of the most commonly prescribed agents for patients with osteoarthritis in some Asian and European countries (23-26). Two systematic reviews of observational studies suggest that the risk of gastrointestinal complications with aceclofenac is comparable to that of celecoxib and lower than that of traditional NSAIDs (27, 28).

Despite the long time elapsed since its discovery, published studies have not defined a clear place for the use of aceclofenac in the treatment of osteoarthritis. This systematic review determines the efficacy and safety of aceclofenac versus other NSAIDs or pain relief medications in osteoarthritis.

## Material and Methods

### Selection criteria

We only included randomized controlled trials of aceclofenac that were single- or double-blinded, and comparative. The trials selected included only patients (any age, either sex) with osteoarthritis of the knee joint confirmed either clinically or radiologically or both; and evaluated the efficacy and/or safety of oral therapy. Finally, all trials included in this study were published in English. We excluded studies if they evaluated other types of arthritis (e.g., rheumatoid arthritis), compared different aceclofenac formulations, if they were publications other than a research article (e.g., review articles, meta-analysis, conference abstract), or if they were multiple or duplicate publications.

This meta-analysis did not require ethical approval. This study did not include confidential data from participants, and there were no interventions.

### Type of interventions

Studies that evaluated the efficacy and/or safety of aceclofenac compared with control interventions (NSAIDs or acetaminophen). We did not consider placebo, opioid analgesics, NSAID combinations, and topical analgesic preparations for control interventions.

### Type of outcome measures

#### Efficacy outcomes

The efficacy outcomes were the improvement in knee pain and function. In case of multiple time points, we extracted the data corresponding to the end of the treatment period. If using multiple pain and function scales, we extracted the data according to the highest order in the earlier literature (29, 30).

#### Safety outcomes

The safety outcomes were the number of participants with adverse events (overall and gastrointestinal) and the total number of withdrawals (overall, adverse events, gastrointestinal adverse events, serious adverse events and inefficacy).

#### Study identification

Two reviewers independently searched the publications in PubMed, Google Scholar, Cochrane systematic review database, clinical trial registry (clinicaltrials.gov) and bibliographies of relevant articles. The search key terms were: "aceclofenac," AND "osteoarthritis," AND ("randomized controlled trial" OR "clinical trial" OR "controlled clinical trial"). We did not use time period restriction and ran the last search

on 20<sup>th</sup> April 2016. We assessed title, abstract and, if required, full articles for eligibility. Any discrepancies (blinding status, comparability of baseline data, etc.) were resolved by discussion and consensus.

### Risk of bias assessment

We assessed the risk of bias in the included trials according to the randomization method (allocation sequence generation and allocation concealment), blinding of investigators, blinding of patients, outcome assessment, incomplete outcome data, selective reporting and other biases. We resolved any disagreements by categorizing the items into low, unclear, and high risk of bias after discussion and consensus.

### Data extraction

We extracted the data for publication year, study period, population, number of study centers, study design, study size, follow-up duration, experimental, and control interventions (generic name, dosage, frequency, and route of administration), wash-out period, treatment duration, participant characteristics (mean age, gender, joints involved, osteoarthritis type), efficacy (pain- and function-related outcome parameters), safety-related outcomes, rescue medications, intention to treat analysis, and financial support. We entered the data in a Microsoft Excel sheet, 2010 (Microsoft corporation; Redmond, Washington, United States) and cross-checked their accuracy.

### Data synthesis

We summarized continuous outcome data as standardized mean differences (SMD) with 95% confidence intervals (CI). We interpreted SMD of pain outcome in terms of improvement according to a 10-cm VAS scale (e.g., SMD of -0.20 corresponds to pain difference of 0.5 cm on the VAS scale), and function outcome as standardized WOMAC disability score (0 to 10) (31). We considered a SMD of 0.2 as a small effect, 0.5 a moderate effect, and 0.8 a large effect (32). We transformed SMDs into odds ratios (OR) to derive the number needed to treat to benefit (NNTB), as the number needed to treat to cause one additional treatment response on knee pain or function as compared with control analgesics. We assumed a control risk of 50% improvement in pain score for the NNTB estimation.

We summarized binary outcomes as risk ratios (RR) with a 95% CI. We computed the number needed to treat (NNT) to cause one additional adverse outcome from the RR. We assumed a control risk of 300 adverse events per 1000 participants to derive the NNT for the safety outcome.

**Table 1.** General characteristics of randomized controlled trials comparing aceclofenac with other analgesics in patients with knee osteoarthritis

Study	Design	Total no. of participants randomized/completed	Number of Male/Female	Drug, dose, and number of participants randomized/completed		Study duration (weeks)	Type of osteoarthritis
				Aceclofenac	Comparator		
Kornasoff et al. (40)	Parallel, multicenter, double-blinded RCT	334/280	134/240	100 mg bid (n=190/145)	Naproxen 500 mg bid (n=184/135)	12	Not specified
Ward et al. (41)	Parallel, multicenter, double-blinded RCT	397/261	173/224	100 mg bid (n=200/138)	Diclofenac 50 mg tid (n=197/123)	12	Not specified
Pareek et al. (42)	Parallel, multicenter, double-blinded RCT	247/240	82/165	100 mg bid (n=125/122)	Diclofenac 75 mg bid (n=122/118)	8	Primary
Pareek et al. (43)	Parallel, multicenter, double-blinded RCT	591/506	200/391	100 mg bid (n=297/254)	Diclofenac 50 mg tid (n=292/254)	6	Primary
Patil et al. (44)	Parallel, single center, single-blinded RCT,	140/118	54/86	100 mg bid (n=70/60)	Diclofenac 75 mg bid (n=70/58)	8	Primary
Sehgal et al. (45)	Parallel, single center, double-blinded RCT	60/60	21/39	100 mg bid (n=30/30)	Diclofenac 50 mg tid (n=30/30)	8	Primary
Perez Busquier et al. (46)	Parallel, multicenter, double-blinded RCT	240/186	21/219	100 mg bid (n=123/103)	Piroxicam 20 mg od (n=117/99)	8	Primary
Torri et al. (47)	Parallel, center not specified, double-blinded RCT	205/179	78/127	100 mg bid (n=103/89)	Piroxicam 20 mg od (n=102/90)	12	Primary
Batlle-Gualda et al. (48)	Parallel, multicenter, double-blinded RCT	168/146	28/140	100 mg bid (n=82/77)	Acetaminophen 1000 mg tid (n=86/69)	6	Primary

RCT: randomized controlled trial

**Table 2.** Quality assessment as per GRADE approach

Outcomes	No. of studies (Design)	Limitation	Inconsistency	Indirectness	Imprecision	Publication bias	SMD (95% CI)	RR (95% CI)	Quality
Pain	Seven (RCT)	Unclear concealment in 3 studies <sup>a</sup>	Serious limitations (p<00001, I <sup>2</sup> = 88%)	No serious indirectness	No serious imprecision	Most studies industry funded & asymmetrical funnel plot <sup>b</sup>	-0.30 (-0.62, 0.01)	-	L
Physical function	Eight (RCT)	Unclear concealment in 4 studies <sup>a</sup>	Serious limitations (p<00001, I <sup>2</sup> = 81%)	No serious indirectness	No serious imprecision	Most studies industry funded & asymmetrical funnel plot <sup>b</sup>	-0.27 (-0.50, -0.03)	-	L
AEs	Seven (RCT)	Unclear concealment in 3 studies <sup>a</sup>	No serious inconsistency	No serious indirectness	No serious imprecision	Most studies industry funded & asymmetrical funnel plot <sup>b</sup>	-	0.90 (0.72, 1.12)	M
GI AEs	Four (RCT)	No serious limitation	No serious inconsistency	No serious indirectness	No serious imprecision	All studies industry-funded	-	0.69 (0.57, 0.83)	M
Total withdrawal	Seven (RCT)	Unclear concealment in 2 studies	No serious inconsistency	No serious indirectness	No serious imprecision	All studies industry-funded	-	0.84 (0.67, 1.05)	M
Withdrawal-AEs	Seven (RCT)	Unclear concealment in 2 studies	No serious inconsistency	No serious indirectness	No serious imprecision	All studies industry-funded	-	0.76 (0.51, 1.14)	M
Withdrawal - GI AEs	Five (RCT)	No serious limitation	No serious inconsistency	No serious indirectness	Wide CI	All studies industry-funded	-	1.30 (0.62, 2.74)	L
Withdrawal-inefficacy	Four (RCT)	No serious limitation	No serious inconsistency	No serious indirectness	Wide CI	All studies industry funded	-	0.51 (0.12, 2.14)	L

AE: adverse events; GI: gastrointestinal; RCT: randomized controlled trial; CI: confidence interval; SMD: standardized mean difference; RR: risk ratio; L: low; M: moderate

<sup>a</sup>Concealment not clear in 3 to 4 studies but blinding suggests likelihood of concealment. The final decision was not to rate down for risk of bias. <sup>b</sup>5 out of 7 studies were industry-funded and one partially supported with study medications. There was no evidence of conflict of interest in the studies funded by pharmaceutical companies. It was not possible to compare industry-funded and non-funded studies due to the small size of the sample. Final decision was to rate down for publication bias.

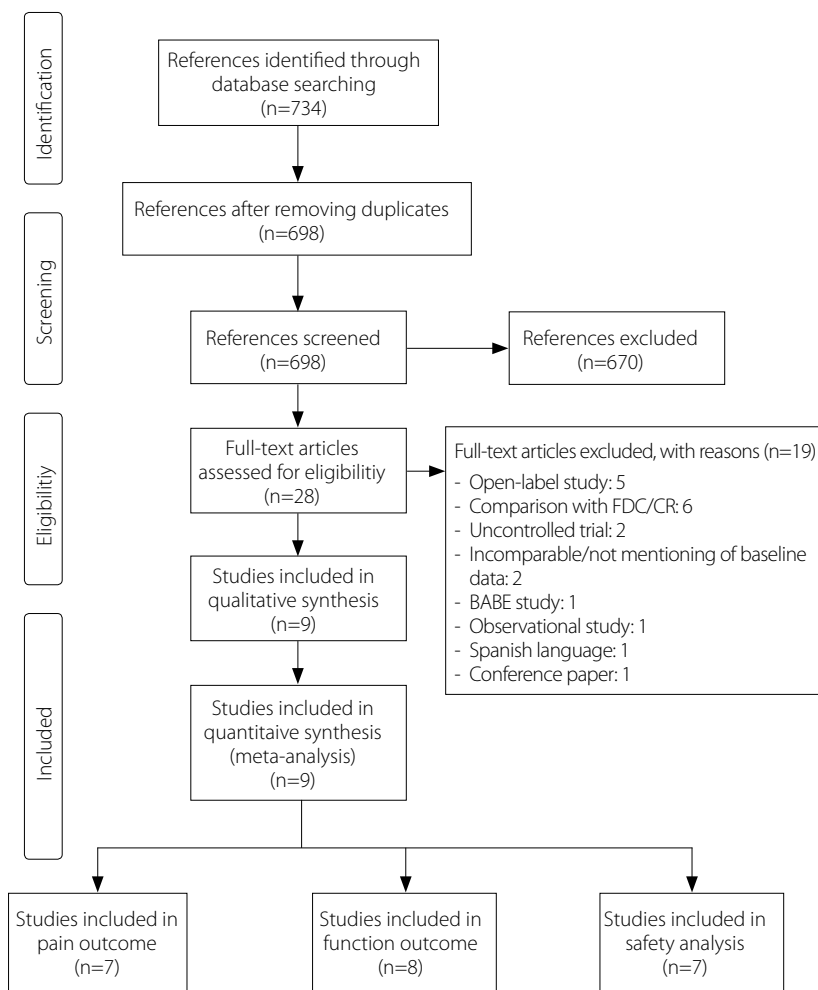


Figure 1. PRISMA flow diagram for study identification

We used the GRADE approach to present the quality of the evidence for efficacy and safety outcomes (32, 33). We checked for study limitations, inconsistencies, indirectness of evidence, imprecision, and publication bias to assess the quality of the evidence (34-38).

We assessed the heterogeneity by the I<sup>2</sup> test (25% was accepted as low, 50% as moderate, and 75% as high) (39). The “funnel plot” of the efficacy outcomes [log (OR)] and its standard error were used to assess publication bias. We visually assessed the “funnel plot” for asymmetry.

We performed the subgroup analyzes of the efficacy outcomes (pain and function) according to the following trial characteristics: type of control analgesics, adequacy of allocation concealment, adequacy of participant blinding, intention-to-treat principle and trial size. A total of 200 randomized patients was used as the criteria to distinguish between small and large trials. Due to the low number of trials, we could not stratify the efficacy outcomes according to funding, duration of treatment and NSAID responsive status.

We pooled the SMDs and RRs by the inverse variance method with random effect model using the “Review manager software version 5.3” (The Nordic Cochrane Centre; The Cochrane Collaboration, Copenhagen, Denmark).

**Results**

**Study characteristics**

From the literature search, we retrieved 9 trials fulfilling the selection criteria (Figure 1). Kornasoff et al. (40) could contribute only to the physical function outcomes due to dichotomous pain data. Ward et al. (41) could not contribute in the efficacy assessment due to dichotomous data of pain and physical function, and we used this trial for the safety assessment only (41). Table 1 shows the general characteristics of all nine included trials, including study design, total number of randomized participants, gender distribution, trial duration, dose, and number of randomized patients for aceclofenac and control drugs (40-48). Control drugs were diclofenac in five trials (41-44, 45), piroxicam in two (46, 47),

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of Participant and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data addressed (Free of attrition bias)	Free of selective reporting (reporting bias)	Free of other Bias
Battle-Gualda 2007	+	+	+	?	+	+	+
Kornasoff 1997	?	?	?	?	+	+	+
Pareek 2006	+	+	+	?	+	+	+
Pareek 2013	+	+	+	?	+	+	+
Patil 2012	+	?	?	-	+	+	?
Perez Busquier 1997	?	?	+	?	+	+	+
Sehgal 2015	?	?	?	?	?	-	?
Torri 1994	?	+	+	?	+	+	+
Ward 1995	+	+	+	?	+	+	+

Figure 2. Risk of bias summary for the included studies. (+) indicates low risk of bias, (?) unclear and (-) a high risk of bias in each item

and acetaminophen (48) and naproxen (40) in one trial each. All included trials except one were double blind (44). Finally, two trials did not specify inclusion of primary or secondary osteoarthritis (40, 41).

**Risk of bias in the included trials**

As shown in Figure 2, both sequence generation and allocation concealment were adequate in four trials (41-43, 48). In Patil et al. (44), only sequence generation was adequate, and in Torri et al. (47), only allocation concealment was adequate. Six trials reported adequate blinding of participants and personnel (41-43, 46-48). No study was deemed adequate with respect to the blinding of outcome assessment. All trials except one were free of attrition bias and selective reporting (45). Sehgal et al. (45) did not report the number of participants at each stage and did not mention the number of patients with gastrointestinal adverse events.

**Efficacy assessment outcomes**

**Knee pain**

A total of seven trials, including 761 participants in the aceclofenac groups and 758 in control analgesic groups, contributed to the knee pain analyzes (Figure 3). In all included trials, primary knee osteoarthritis had been assessed. There was no significant difference in

**Table 3.** Subgroup analysis of pain scale and physical function

Subgroup	Pain scale			Physical function		
	SMD (95% CI)	I <sup>2</sup> (%)	p	SMD (95% CI)	I <sup>2</sup> (%)	p
<b>Type of analgesic control</b>						
Diclofenac	-0.53 (-1.05, 0.00)	92	<0.00001	-0.46 (-0.89, -0.04)	88	<0.00001
Piroxicam	0.12 (-0.16, 0.40)	47	0.17	0.07 (-0.14, 0.27)	0	0.71
Acetaminophen	-0.32 (-0.63, -0.02)	NE	NE	-0.03 (-0.36, 0.29)	NE	NE
<b>Allocation concealment</b>						
Adequate	-0.16 (-0.54, 0.22)	89	<0.00001	-0.45 (-0.75, -0.14)	NE	NE
Unclear	-0.53 (-1.17, 0.12)	88	0.0002	-0.28 (-0.60, 0.05)	85	0.0001
<b>Blinding of participants</b>						
Adequate	-0.13 (-0.43, 0.17)	86	<0.00001	-0.26 (-0.69, 0.17)	82	0.0008
Unclear	-0.83 [-1.25, -0.41]	44	0.18	-0.20 (-0.48, 0.08)	84	<0.00001
<b>Intention to treat analysis</b>						
Yes	-0.29 (-0.74, 0.15)	90	<0.00001	-0.40 (-0.92, 0.12)	80	0.007
Unclear	-0.32 (-0.88, 0.24)	90	<0.00001	-0.37 (-0.78, 0.04)	89	0.0002
<b>Total patient randomized</b>						
Large trial (>200)	-0.09 (-0.44, 0.27)	88	<0.00001	-0.20 (-0.53, 0.13)	78	0.001
Small trial	-0.63 (-1.07, -0.18)	74	0.02	-0.12 [-0.39, 0.14]	81	0.0003

SMD: standardized mean difference; CI: confidence interval; NE: not estimable

knee pain reduction between aceclofenac and control interventions [SMD: -0.30 (-0.62, 0.01); I<sup>2</sup>=88%]. This corresponds to a difference in pain score of 0.75 cm (95% CI: 1.55, -0.02) on a 10-cm VAS scale. The NNTB to cause one additional treatment response on knee pain, as compared to control analgesics, was 8 (95% CI: 4, -221) participants. As shown in table 2, the GRADE approach suggests low quality evidence. On visual inspection, we observed an asymmetrical funnel plot.

As shown in table 3, we observed benefits for aceclofenac in comparison to acetaminophen [SMD: -0.32 (95% CI: -0.63, -0.02)]. This corresponds to a difference in pain score of 0.8 cm on a 10-cm VAS scale. We observed larger benefits for aceclofenac in trials with unclear blinding of the participants [SMD: -0.83 (95% CI: -1.25, -0.41)] and smaller trials [SMD: -0.63 (95% CI: -1.07, -0.18)].

#### Knee physical function

A total of eight trials, including 809 participants in the aceclofenac groups and 900 in control analgesic groups, contributed to knee physical function analyzes (Figure 3). Aceclofenac was more effective than control analgesic interventions in improving knee physical functions [SMD: -0.27 (-0.50, -0.03); I<sup>2</sup>=81%; GRADE

approach evidence quality- low]. This corresponds to a difference in function score of 0.67 cm (95% CI: 1.25, 0.07) on a 10-cm VAS scale. The NNTB to cause one additional treatment response on knee function, as compared to control analgesics, was 8 (95% CI: 5, 74) participants. The funnel plot was asymmetrical on visual inspection. Kornasoff et al. (40) did not specify inclusion of primary or secondary osteoarthritis. In any case, physical function outcome did not change upon exclusion of this trial [SMD: -0.30 (-0.57, -0.03); I<sup>2</sup>=83%].

As shown in table 3, we evaluated the benefits for aceclofenac in comparison to diclofenac [SMD: -0.46 (95% CI: -0.89, -0.04)] and acetaminophen [SMD: -0.45 (95% CI: -0.75, -0.14)]. This corresponds to a difference in pain score of 1.15 and 1.12 cm on a 10-cm VAS scale compared to diclofenac and acetaminophen, respectively. Again, we observed larger benefits for aceclofenac in small trials [SMD: -0.56 (95% CI: -0.85, -0.26)].

#### Safety outcomes

##### Tolerability

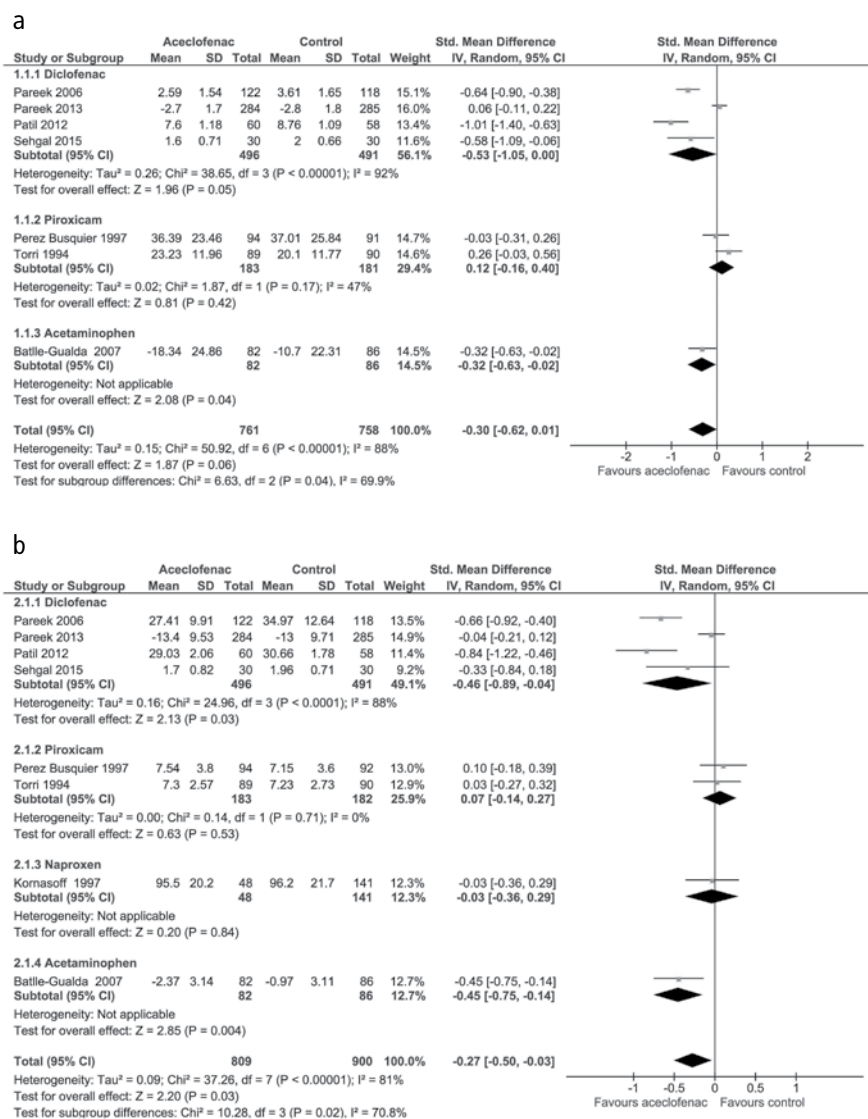
Seven trials reported a total of 306 adverse events in 1039 participants of the aceclofenac groups, and 341 adverse events in 1032 participants of control analgesic groups (Figure 4).

We found no significant difference in adverse events occurrence between aceclofenac and control groups [RR 0.90 (95% CI: 0.72, 1.12); I<sup>2</sup>=58%; GRADE approach evidence quality- moderate].

Four trials reported 162 gastrointestinal adverse events in 707 participants of the aceclofenac groups, and 234 in 704 participants of the control analgesic groups (Figure 4). Participants were 31% less likely to experience gastrointestinal adverse events in aceclofenac groups compared with control analgesic groups [RR 0.69 (95% CI: 0.57, 0.83); I<sup>2</sup>=12%; GRADE approach evidence quality- moderate]. The NNTB to cause one additional participant to experience fewer gastrointestinal adverse events, as compared to control analgesics, was 11 (95% CI: 8, 20).

##### Withdrawal rate

Seven trials reported the withdrawal of 135 out of 1104 participants in the aceclofenac groups, and 162 of 1096 participants in the control groups (Figure 4). We observed no significant difference in the dropout rate between aceclofenac and control groups [RR 0.84 (95% CI: 0.67, 1.05); I<sup>2</sup>=9%; GRADE approach evidence quality- moderate]. On the subgroup analyzes, aceclofenac did not show any significant dif-



**Figure 3. a, b.** Forest plot of the comparison between aceclofenac and control interventions for the efficacy outcome a) pain scale b) physical function

ference in withdrawal rate in comparison to diclofenac [0.80 (95%CI: 0.58–1.10), I<sup>2</sup>=0%], piroxicam [1.06 (95%CI: 0.67–1.68), I<sup>2</sup>=0%] and naproxen [0.89 (95%CI: 0.63–1.26)]. By contrast, aceclofenac showed significantly less withdrawal than acetaminophen [0.31 (95%CI: 0.12–0.80)]. We found little difference in dropout rate due to overall adverse events [RR 0.76 (95% CI: 0.51, 1.14); GRADE approach evidence quality- moderate], gastrointestinal adverse events [RR 1.30 (95% CI: 0.62, 2.74); GRADE approach evidence quality- low] and inefficacy [RR 0.51 (95% CI: 0.12, 2.14); GRADE approach evidence quality- low] between aceclofenac and control analgesics.

**Discussion**

In this meta-analysis, we observed benefits for aceclofenac in terms of improvement of knee function in patients with osteoarthritis. We did not find significant differences between ace-

clofenac and control analgesics in terms of alleviating pain intensity. Gastrointestinal adverse events are an important limitation of long-term NSAID use in osteoarthritis. We observed less risk of gastrointestinal adverse events with aceclofenac. However, the reporting of this result is incomplete and based on only half of the trials included in the meta-analysis. Aceclofenac did not differ from other NSAIDs in terms of overall tolerability and withdrawal rate.

Diclofenac was the most common control drug in this meta-analysis. This may be because of its widespread use as a reference drug in osteoarthritis trials (19). Recent evidence suggest diclofenac (150 mg/day) as one of the most effective NSAIDs in alleviating pain (13, 14). The literature also suggests that acetaminophen is the least effective analgesic, irrespective of the dose (13, 14, 49). All included studies in this meta-analysis used diclofenac (150 mg/

day). Aceclofenac (100 mg/day) showed small to moderate benefit for alleviating pain intensity and improving function over diclofenac (150 mg/day) and acetaminophen (3000 mg/day). This finding should be interpreted in terms of evidence based on few studies for the subgroup analysis. Moreover, we could not have the comparative effect of different doses and duration of treatment due to paucity of data. We also observed a larger benefit of aceclofenac for alleviating pain intensity in studies with unclear blinding of participants (44, 45). This suggests the possibility of performance bias. However, the function outcome was not affected by the adequacy of participant blinding. We also found moderate benefit of aceclofenac for pain intensity and function outcomes in subgroup analyzes with small sample studies (44, 45, 48). This finding is in accordance with an earlier meta-epidemiological study suggesting the high possibility of clinically relevant and statistically significant treatment benefit for small trials in osteoarthritis (50). This may have skewed the overall effect on function outcome.

Safety data analysis suggest that there is no difference between aceclofenac and other NSAIDs for the occurrence of overall adverse events and withdrawal rate. However, we observed lower rate of withdrawal in the aceclofenac group as compared to acetaminophen. The gastrointestinal adverse events are an important safety challenge for osteoarthritis patients receiving NSAIDs. Gastrointestinal protection is an important strategy to enhance compliance during long-term NSAID use (51). We found significantly less risk of gastrointestinal adverse events with aceclofenac compared with other NSAIDs. This is in line with previous systematic reviews (27, 28). The evidence quality is moderate according to the GRADE approach, as all studies providing gastrointestinal adverse outcomes were industry-funded. None of the trials included in our meta-analysis was longer than 3 months. The risk of gastrointestinal adverse events increases with duration of treatment (52). Patients are expected to take NSAIDs for longer in routine care and a duration of three months is too short to predict gastrointestinal safety. Moreover, the good gastrointestinal tolerability profile of aceclofenac did not result in a reduced withdrawal rate. We could not assess other important safety issues associated with long-term NSAIDs use, such as risk of hypertension, myocardial infarction, stroke, congestive heart failure, and renal failure (16, 17, 53).

Although we meticulously search broad literature databases such as “PubMed” and “Google Scholar,” the possible source of selection

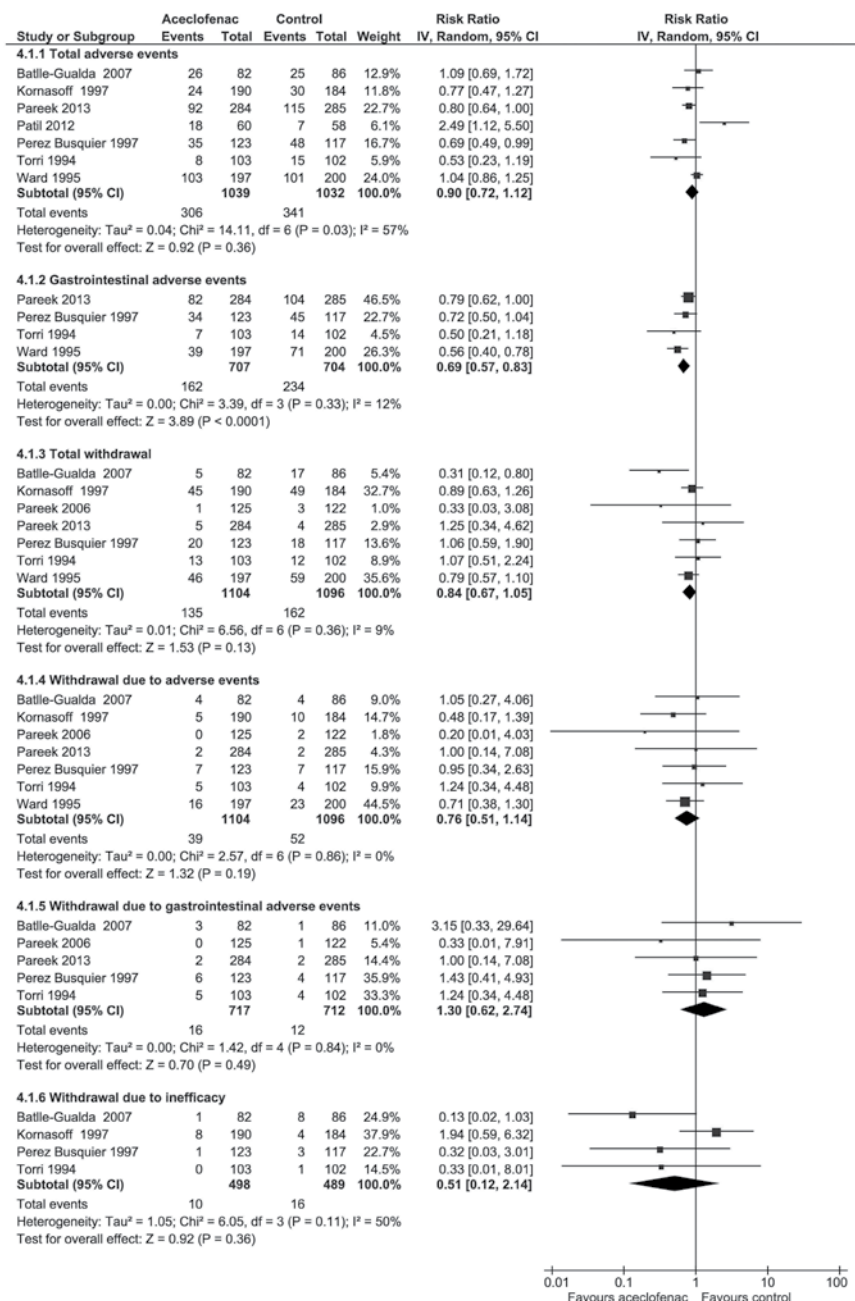


Figure 4. Forest plot of the comparison between aceclofenac and control interventions for the safety outcome

bias could be having been restricted to publications written in English. We had to exclude two trials due to the pain outcome and one trial due to the function. We did not try to find the unpublished studies. We performed various subgroup analyzes to evaluate the heterogeneity. Heterogeneity could not be explained by variables such as type of analgesic control, allocation concealment, blinding of participants, intention to treat analysis or trial size. The possible reason for the persistent heterogeneity could have been the lack of subgroup analysis of important parameters such as NSAID responsive status and duration of treatment.

The effect of aceclofenac over other analgesics was significant for function improvement and gastrointestinal adverse events. The evidence is based on short-term trials only ( $\leq 3$  months). The overall effect seems small and may be biased due to high heterogeneity, effect of small trials and methodological issues.

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